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A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis[1]

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Summary

Objective: To resolve uncertainty regarding sex differences in osteoarthritis (OA) by performing a meta-analysis of sex differences in OA prevalence, incidence and severity.

Methods: Standard search strategies for population-based studies of OA providing sex-specific data. Random effects meta-analysis to provide pooled male vs female risk and rate ratios for prevalent and incident OA, and standardized mean differences (SMD) for OA severity. Meta-regression was used to investigate sources of heterogeneity.

Results: Males had a significantly reduced risk for prevalent OA in the knee [Risk Ratio (RR) 0.63, 95% CI 0.53–0.75] and hand [RR 0.81, 95% CI 0.73–0.90] but not for other sites. Males aged <55 years had a greater risk of prevalent cervical spine OA [RR 1.29, 95% CI 1.18–1.41]. Males also had significantly reduced rates of incident OA in the knee [Incidence Rate Ratio (IRR) 0.55, 95% CI 0.32–0.94] and hip [IRR 0.64, 95% CI 0.48–0.86], with a trend for hand [IRR 0.65, 95% confidence interval (CI) 0.35–1.20]. Females, particularly those ≥ 55 years, tended to have more severe OA in the knee but not other sites. Heterogeneity in the estimates of sex differences in prevalence was substantially explained by age and other study design factors including method of OA definition.

Conclusions: The results demonstrate the presence of sex differences in OA prevalence and incidence, with females generally at a higher risk. Females also tend to have more severe knee OA, particularly after menopausal age. The site differences indicate the need for further studies to explore mechanisms underlying OA.

Key words: Sex differences, Osteoarthritis, Population-based.

Introduction

Osteoarthritis (OA) is a major public health problem due to its high prevalence, costs, and levels of pain and disability. Efforts are underway to identify causal mechanisms responsible for the development of OA. While risk factors such as age, obesity, injury and genetic profiles have been identified, the role of sex in OA is unclear[1,2]. The study of sex differences in OA may provide insights into disease mechanisms in OA. It is reported in the literature that women have a higher prevalence of knee and certain types of hand OA than men, particularly after 50 years of age[3–5], whereas the evidence for a sex difference in hip OA is conflicting from individual study results. The majority of studies providing data on sex differences deal with prevalent OA, with very few examining sex-specific OA incidence[6–9]. Moreover, it is unclear whether any observed sex difference is due to reporting differences or a true difference in radiographic OA (ROA) or whether the severity of OA differs between sexes. The aim of this study therefore was to use meta-analysis and meta-regression to study site-specific sex differences in prevalence, incidence and severity of OA.

Methods

LITERATURE SEARCH

A MEDLINE search (1966–2003) was conducted using the terms ''Sex and OA'', ''Gender and OA'' and ''OA prevalence'', and ''OA incidence''. References from retrieved publications were manually checked for any additional studies of OA and review articles on OA epidemiology. Reports from the National Center for Health Statistics (USA) were obtained for data regarding the major health surveys of chronic diseases including the Health Examination Survey (HES)[10] and the National Health and Nutrition Examination Survey (NHANES-I)[11]. These

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strategies were supplemented by a further electronic search for specific terms linking OA with different joint sites (i.e., knee, hand, hip and spine). Published studies were included in the meta-analysis if they provided numbers or rates of males and females affected by OA and were population-based. Hospital or clinic-based series were excluded due to the possibility of selection bias affecting associations in such studies. One non-English paper was identified[12], and was excluded to facilitate data extraction and quality assessment.

EXTRACTION OF DATA

Two persons (VS, GZ) independently extracted data. In prevalence studies numbers of males and females with OA and the number in the sample at risk in either sex were identified. In studies where only prevalence rates were reported, numbers with OA in either sex were calculated based on reported rates and the sample at risk. When age-stratified data were provided, numbers of affected males and females were extracted according to arbitrary age categories (age <55 years, age ≥ 55 years) based on previous reports describing variation in sex-specific risk[3] as well as convenience of assigning age categories in the included studies. Incidence rates were obtained for males and females from the included OA incidence studies. Grades of severity stratified by site were also obtained if reported.

ASSESSMENT OF QUALITY

Quality of the papers was assessed by one of the study investigators (TW) independent of data extraction using a framework modified from previous work[13]. Studies were ranked by *a priori* characteristics that would be likely to minimize bias in results. These included: sampling procedure (0, not stated; 1, non-random; 2, random); sample response rate (0, not stated; 1, $<50\%$; 2, $\geq 50\%$); definition of OA (0, self-report; 1, clinical diagnosis; 2, X-ray scale); use of radiographic atlas (0, no; 1, yes); reporting of reliability of OA definition (0, no; 1, yes) with a maximum possible quality score of 8. The category of clinically diagnosed OA included mostly studies depending solely on clinical findings (*based on clinical joint examination*)[14–17], one study using clinician reported arthritis[18] and one study using a combination of X-ray and clinical findings[19].

STATISTICAL ANALYSIS

The Cochrane Review Manager 4.2 software (MetaView, version 4.2) was used for this meta-analysis. For the meta-analysis of OA prevalence, the outcome measure was the risk ratio (RR) that refers to the ratio of the prevalence of OA among males to the prevalence of OA among females. In prevalent peripheral joint OA, stratified analyses were conducted according to pre-specified variables including age, OA definition, ethnicity, sample type (random, non-random), response rate, and provision of diagnostic reliability. The few studies where age-stratified data could not be extracted were analyzed in a category termed 'unstratified'[15,18,20–23]. In spine OA, analyses were performed separately for spine apophyseal OA and spine disc degeneration (SDD) in both cervical and lumbar regions. Due to the small number of studies on spine disease, stratified analyses were performed only according to age categories.

For incident OA, the outcome measure was the unadjusted incidence rate ratio (IRR), which was the ratio of the incidence for males relative to females. If this was unavailable, the ratio of cumulative incidences was used. The number of incident cases and person-years of follow-up were provided for both sexes in one study of radiographic hand, hip and knee OA allowing computation of incidence rates[8]. Similar information could be derived from the data reported in a medical record-linkage study of symptomatic radiographic knee and hip OA[9]. In two studies, sex-specific cumulative incidence rates were provided[24,25]. In one report, male vs female relative risk (RR) estimates from a Cox-model were used for the meta-analysis with standard errors derived from the confidence intervals (CI) provided[7].

For the analysis of sex differences in OA severity, the outcome measure was the standardized mean difference (SMD) in reported severity grades between males and females. In all but one of the studies using radiographs, grading of severity had been performed using the Standard Radiographic Atlas of Arthritis[26] as OA absent (grade 0), dubious (grade 1), mild (grade 2), moderate (grade 3) and severe (grade 4). In these studies, categories of grade 0 or 1 were assigned a score of 0.5, radiographs of grade 2 were assigned a score of 2, and radiographs of grade 3 or 4 were assigned a score of 3.5. In one remaining radiographic study[11] in which there had been a subjective grading of radiographs, we arbitrarily assigned normal/questionable OA a score of 0.5, minimal OA a score of 2, and moderate/severe OA a score of 3.5. In the only study using a clinical grading[17], we assigned a score of 0.5 to absent/minimal OA, a score of 2 to moderate OA, and a score of 3.5 to severe OA. For each study, the mean and standard deviation of the assigned severity score for males and females was then computed. The SMD in severity between males and females for each study was then computed using standard methods in the Cochrane Review Manager 4.2 software (MetaView, version 4.2). The formula for SMD is as follows:

$$\mathrm{SMD} = \left(\frac{m_{1i} - m_{2i}}{s_i}\right)\left(\frac{1-3}{4N_i - 9}\right)$$

where m refers to individual group mean, s_i is the pooled standard deviation, and N_i is the pooled sample size of the two groups.

Outcome measures were pooled across studies using a random effects model which allows for heterogeneity of effects between studies[28]. Tests for homogeneity were performed, and statistical heterogeneity reported as the ratio (in percentage) of between-study variation to the total variation in effect estimate according to the method described by Higgins *et al.*[29]. A larger ratio indicates greater heterogeneity between studies. Publication bias was examined graphically using a funnel plot of study precision (standard error of natural logarithm of risk ratio, lnRR) against effect size (risk ratio) for prevalent peripheral OA but not spine OA or incident OA given the paucity of studies in these categories. In the absence of significant publication bias, the funnel plot of study precision vs effect size should assume a symmetrical funnel shape with the apex pointing upwards. A deficiency in the base of the funnel with non-symmetry indicates the presence of possible publication bias from unpublished small studies.

Weighted random effects meta-regression[27] was used to explore heterogeneity between studies of prevalent OA at

different sites (except for sites of spine disease due to small numbers of studies in this category). The natural logarithm of the RR (lnRR) weighted by inverse variance for each study was regarded as the dependent variable and the effect of a number of explanatory variables (including age, OA definition, ethnicity, sample type, response rate and diagnostic reliability) was examined. STATA version 8 (Stata Corporation, Texas, USA, command 'metareg')[27] was used to provide regression coefficients and an iterative estimate of residual between-study heterogeneity (τ^2). Multivariable models for each OA site were fitted to examine the independent effect of the explanatory variables using a step-wise approach, using change in τ^2 as an indicator of best-fit. Age was not used as a covariate in the multivariable analysis to avoid duplication of study units from stratification. After transformation back to the original ratio scale, the meta-regression estimate is a ratio of the average RR reported by studies with one characteristic (e.g., radiographic definition) to the average RR reported by studies with another characteristic (definition by self-report). Univariable meta-regression was also used to explore heterogeneity in the analysis of OA severity using age, sampling response, reliability of diagnosis and ethnicity as explanatory variables. Meta-regression was not attempted for incidence analysis given the paucity of studies.

Results

SEARCH RESULTS

A total of 178 journal articles were screened after the initial MEDLINE and hand-search. Sixty-eight studies were identified as providing OA prevalence data for males and females of which 28 were excluded from the analysis (17 hospital-based studies, three colon radiograph-based studies, six studies in highly selected skeletal samples, one hospital register cohort study and one published in Japanese). Of the remaining 40 population-based studies[10,11,13–23,30–55] six more were excluded[35,41,43,45,46,50]. Reasons for their exclusion were: specific numbers for males and females were unavailable from three studies[41,45,46], data overlapped with other included reports in two studies[35,43], and radiographs were obtained only for a selected sub-sample in one study[50]. The final meta-analyses for prevalence were performed on 34 studies with some studies reporting on OA in multiple joint sites. Relevant characteristics of all included studies of OA prevalence are shown in Table I. The search for papers regarding OA incidence generated nine studies of interest[7–9,24,25,56–59], of which four hospital-based studies were excluded[56–59]. The characteristics of the five included incidence studies are shown in Table II.

Table I
Included studies of prevalent osteoarthritis

First author	Sample size	Study population (age)	Sites of OA	OA diagnosis	Quality score*
Acheson[30]	685	Connecticut, USA (21+)	Any OA, Hand	X-ray	4
Bagge[31]	340	Goteborg, Sweden (70–79)	Hand, knee	X-ray	8
Blumberg[32]	355	Alaskan Eskimo (20+)	Hand	X-ray	4
Bremner[23]	528	Jamaica (35–65)	Any OA, spine	X-ray	7
Brighton[33]	543	Rural Black African (20+)	Any OA	X-ray	7
Butler[34]	3035	Tecumseh, USA (16+)	Hand	X-ray	8
Carmona[14]	2192	Spain (20+)	Hand, knee	Clinical	5
Cvitejic[20]	610	Zagreb, Croatia (45+)	Hand, knee, hip	X-ray	8
Dodge[36]	4407	Tecumseh, USA (16+)	Hand, spine	X-ray	7
Felson[37]	598	Framingham, USA (60+)	Knee	X-ray	6
Forman[17]	682	New York, USA (60+)	Knee	Clinical	2
Haara[22]	3595	Finland	Hand	X-ray	8
HES 1960–1962[10]	7132	USA (18+)	Hand	X-ray	7
Hirsch[38]	755	Pima Indian, USA (45+)	Hip	X-ray	4
Jones[39]	1273	Dubbo, Australia (60+)	Any OA	Self-report	5
Jones[13]	300	Dubbo, Australia (60+)	Spine	X-ray	4
Kellgren[40]	380	Lancashire, UK (55–64)	Any OA, spine	X-ray	8
Laine[19]	539	Finland (55+)	Hand	X-ray + symptoms	4
Lawrence[21]	2296	UK (15+)	Any OA, all sites	X-ray	7
Lawrence[42]	3947	UK (15+)	Spine	X-ray	5
Lethbridge-Cejku[44]	898	Baltimore, USA (20+)	Knee	X-ray	5
Meyers[47]	162	Black African	Any OA	X-ray	5
Mikkelsen[16]	4688	Tecumseh, USA (20+)	Any OA	Clinical	5
Nevitt[48]	1492	Beijing, China (60+)	Hip	X-ray	8
NHANES-I [11]	6913	USA (25–74)	Knee, hip	X-ray	7
Odding[49]	2895	Netherlands (60+)	Knee, hip	X-ray	7
Pogrund[51]	641	Jerusalem, Israel (45+)	Hip	X-ray	5
Solomon[15]	300	Black South African (35+)	Hand, hip, knee	X-ray (hand, hip)	5
Steven[18]	35,251	Scotland, UK (20+)	Any OA	Clinical	3
Van Saase[52]	6585	Netherlands (20+)	All sites	X-ray	8
Zhang[55]	2507	Beijing, China (60+)	Hand	X-ray	8
Zhang[55]	1628	Framingham, USA (60+)	Hand	X-ray	8
Zhang[53]	1032	Framingham, USA (70+)	Hand	X-ray + symptoms	6
Zhang[54]	1781	Beijing, China (60+)	Knee	X-ray	8

HES, Health Examination Survey; NHANES, National Health and Nutrition Examination Survey; USA, United States of America; UK, United Kingdom.

*Scores range from 0 to 8; higher scores indicate better quality; depending on selection of sample, OA definition, use of standard X-ray atlas, response rate and diagnostic reliability.

Table II
Included studies of incident osteoarthritis

Study	Sample	Definition of incident OA	Joints	Comments
Oliveria *et al.*[8]	Fallon community health plan members, 1998–1992, age range 20–89 years	First evidence of radiographic OA (K&L grade ≥ 2) plus joint symptoms	Knee, hip, hand OA	Results presented as sex-specific incidence rates per 100,000 person-years for 10-year age intervals
Wilson *et al.*[9]	Residents of Rochester, Minnesota, 1985, age ≥ 30 years	Symptomatic radiographic OA	Knee, hip OA	Results presented as sex-specific incidence rates per 100,000 person-years for 10-year age intervals
Manninen *et al.*[7]	10-year follow-up study of a cohort of Finnish farmers, $n = 6647$, age range 40–64 years	Radiographic OA (K&L grade ≥ 2) identified from disability pension medical certificates.	Knee OA	Cases reflect disabling OA. Results presented as incidence rate per 100,000 person-years for the entire sample. No sex-specific rates available. Adjusted relative risks given for women vs men
Felson *et al.*[24]	Framingham cohort, $n = 869$, 10-year follow-up, age range	Radiographic OA (K&L grade ≥ 2)	Knee OA	Results presented as rate ratio for women vs men, and for age <70 and age >70
Chaisson *et al.*[25]	1967 Framingham cohort, $n = 751$, 24-year follow-up	Radiographic OA at each hand joint (K&L grade ≥ 2), only in right hand	Hand OA	Results presented as cumulative incidence expressed as percentage of subjects eligible for incident disease

K&L, Kellgren and Lawrence Standard Radiographic Atlas.

Fourteen studies providing sex-specific numbers of people with prevalent OA graded by severity were identified[10,11,15,17,21,31,36–38,44,49,52,54,55] and are presented in Table I. Nine studies provided data for knee OA[11,17,21,31,37,44,49,52,54], six for hip OA[11,15,21,38,49,52] and five for hand OA[10,21,31,36,55], with some studies providing data for more than one site.

SEX DIFFERENCES IN PREVALENCE OF OA

Meta-analysis

Results of meta-analyses for prevalent OA are shown for peripheral and any OA in Table III and Fig. 1, and for spine disease in Table IV and Fig. 2. For any OA, data from nine studies ($n = 51{,}761$) were available with an overall

Table III
Sex differences in prevalent peripheral and any OA—overall pooling and by factors of interest

	Any OA			Knee OA			Hip OA			Hand OA		
	*n**	RR†	95% CI	*n*	RR	95% CI	*n*	RR	95% CI	*n*	RR	95% CI
Overall estimate‡	9	0.93	0.80–1.08	12	**0.63**	**0.53–0.75**	9	1.18	0.91–1.52	13	**0.81**	**0.73–0.90**
By factors												
Age												
<55 years	5	0.98	0.73–1.31	5	0.82	0.65–1.03	3	1.04	0.62–1.77	6	1.03	0.88–1.21
≥ 55 years	8	0.92	0.80–1.05	10	**0.65**	**0.55–0.77**	7	1.05	0.87–1.28	11	**0.77**	**0.67–0.89**
Age unstratified	1	**0.78**	**0.72–0.84**	2	**0.50**	**0.34–0.72**	2	**1.83**	**1.04–3.23**	2	**0.80**	**0.75–0.86**
OA definition												
X-ray only	6	1.06	0.94–1.19	11	**0.67**	**0.57–0.79**	9	1.18	0.91–1.52	10	**0.88**	**0.81–0.96**
Other	3	**0.69**	**0.51–0.94**	1	**0.33**	**0.24–0.43**	0	na		3	**0.48**	**0.25–0.91**
Ethnicity												
Caucasian	6	**0.84**	**0.72–0.99**	10	**0.65**	**0.54–0.80**	6	1.12	0.85–1.48	12	**0.79**	**0.70–0.89**
Other	3	1.16	0.86–1.56	2	**0.51**	**0.44–0.59**	3	1.62	0.91–2.89	1	0.95	0.87–1.03
Sample type												
Random	6	0.89	0.74–1.07	10	**0.62**	**0.51–0.76**	8	1.14	0.88–1.49	9	**0.81**	**0.72–0.92**
Non-random	3	1.02	0.73–1.44	2	0.67	0.39–1.15	1	1.69	0.80–3.53	4	0.79	0.54–1.15
Response rate												
≥ 50%	6	0.93	0.77–1.14	10	**0.62**	**0.50–0.76**	6	1.13	0.85–1.51	11	**0.79**	**0.70–0.89**
<50% or not stated	3	0.92	0.74–1.15	2	0.70	0.44–1.11	3	1.44	0.86–2.42	2	1.00	0.89–1.13
Reliability												
Provided	2	0.93	0.86–1.00	7	**0.62**	**0.52–0.75**	4	1.25	0.97–1.62	6	**0.83**	**0.72–0.96**
Not provided	7	0.93	0.77–1.14	5	**0.65**	**0.45–0.94**	5	1.14	0.74–1.76	7	**0.78**	**0.65–0.93**

na, not applicable.
*Number of studies.
†RR, pooled risk ratio (male:female) using random effects meta-analysis; bold face indicates the RR were statistically significant at $\alpha = 0.05$.
‡*P* for heterogeneity for overall pooled estimate in all sites <0.001.

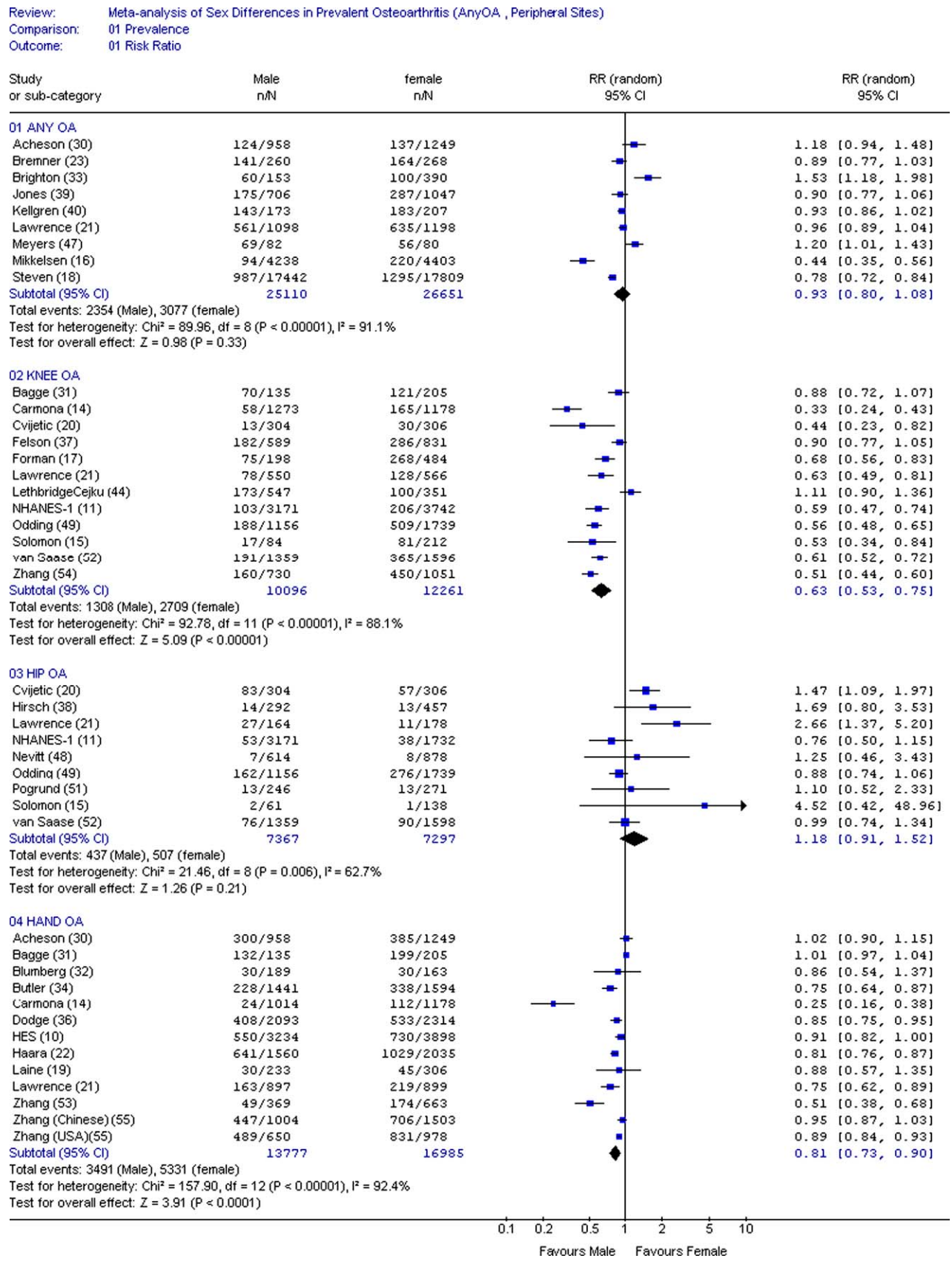

Fig. 1. Sex differences in prevalent OA—studies of any OA and peripheral sites. Studies identified by first author with reference citation number in parentheses.

Table IV
Sex differences in prevalent spine OA—overall pooling and by age

	Disc degeneration						Apophyseal OA					
	C-spine			L-spine			C-spine			L-spine		
	n[*]	RR[†]	95% CI	*n*	RR[†]	95% CI	*n*	RR	95% CI	*n*	RR	95% CI
Overall estimate	4	1.11	0.98–1.26	4	1.09	0.89–1.34	2	1.07	0.89–1.28	2	1.13	0.44–2.85
By age												
<55 years	3	**1.29**	**1.18–1.41**	3	1.10	0.62–1.96	1	**1.72**	**1.18–2.51**	1	0.99	0.96–1.02
>55 years	3	1.24	0.99–1.56	2	1.10	0.92–1.31	1	0.95	0.81–1.11	0	na	na
Age unstratified	1	0.97	0.85–1.10	1	**1.15**	**1.00–1.33**	1	1.23	0.91–1.68	1	1.29	0.98–1.68

P for heterogeneity for overall pooled estimate in all sites <0.001. C-spine, cervical spine; L-spine, lumbar spine; na, not applicable.
[*]Number of studies.
[†]RR, pooled risk ratio (male:female) using random effects meta-analysis ; bold face indicates the RR was statistically significant at $\alpha = 0.05$.

non-significant risk reduction for males (pooled RR 0.93, 95% CI 0.80–1.08) (Table II, Fig. 1). For knee OA (12 studies, $n = 22{,}359$), there was a significant reduction in risk for males (pooled RR 0.63, 95% CI 0.53–0.75). For hip OA (nine studies, $n = 14{,}664$), there was no significant sex difference (pooled RR 1.18, 95% CI 0.91–1.52). In hand OA (13 studies, $n = 30{,}762$), there was a significant risk reduction in males (pooled RR 0.81, 95% CI 0.73–0.90). Only four studies provided data on spine disease (Table III, Fig. 2), with no significant difference in pooled risk estimates for the whole group between males and females for cervical or lumbar spine OA. There was significant

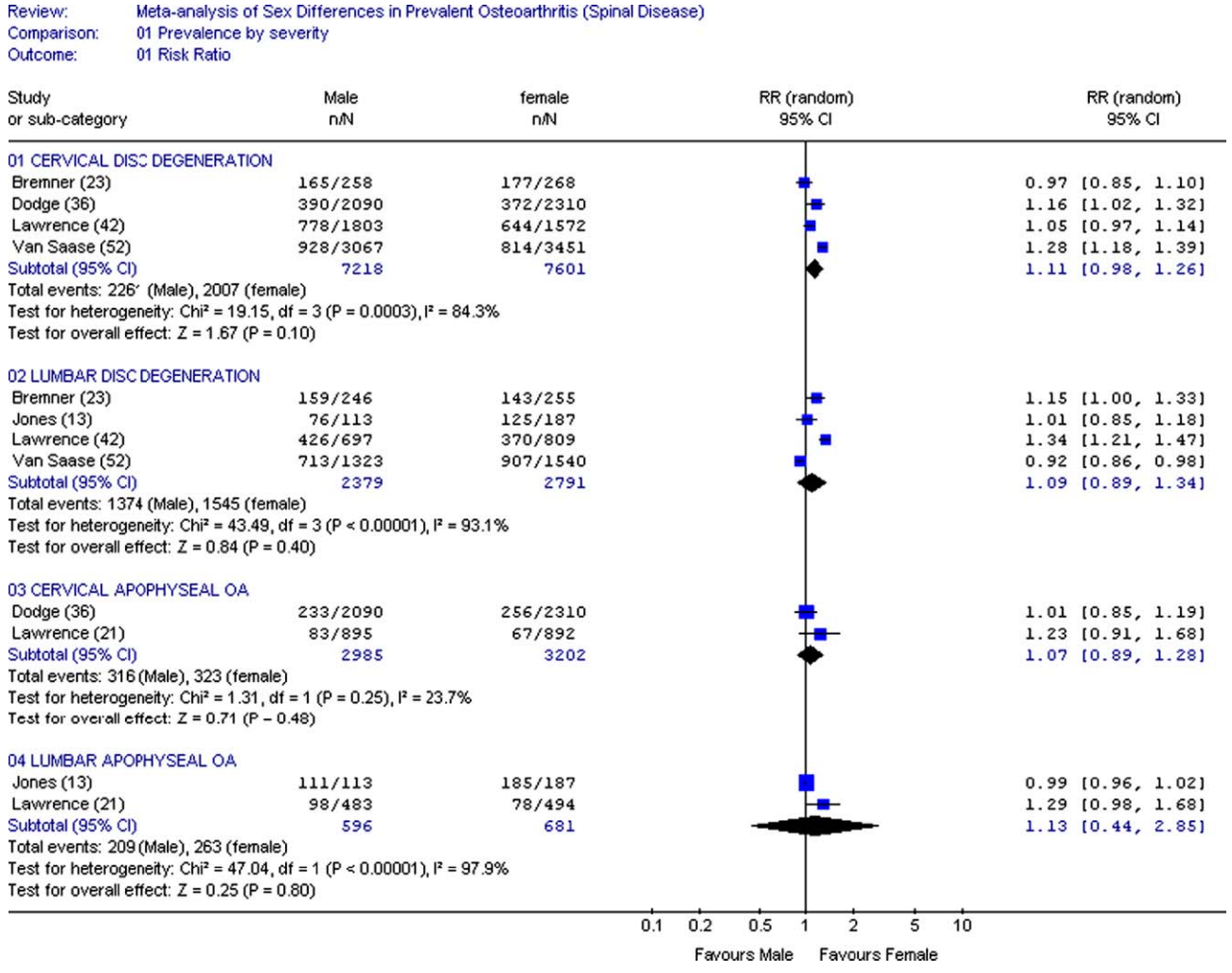

Fig. 2. Sex differences in prevalent OA—studies of spine disease. Studies identified by first author with reference citation number in parentheses.

heterogeneity in the overall pooled male vs female RR estimates in all categories of OA except cervical spine apophyseal OA for which data were available only in two studies. This heterogeneity persisted in most subgroup analyses. Heterogeneity was least for hip OA and became negligible when hip OA studies were pooled by age and ethnicity.

Meta-regression

The magnitude of the male vs female RR varied by age. Among those ≥ 55 years of age, males tended to have a significantly lower pooled risk of knee OA and hand OA compared to females, with no significant sex differences observed for any OA, hip OA and spine disease (Table III). Among those <55 years of age, no significant sex differences were observed in pooled risk estimates for peripheral OA categories and any OA (Table III). There appeared to be a greater pooled risk for cervical spine OA in males among those <55 years of age (Table IV), but not for other sites of spine disease. In univariable meta-regression, age contributed to the variability in lnRR estimates between studies for both knee and hand OA. There was an estimated relative increase in the RR males vs females of $+0.31$ for knee OA ($P = 0.02$) and $+0.30$ for hand OA ($P = 0.04$) for younger (<55 years) compared to older age (≥ 55 years), the effect of this being to decrease sex differences in prevalence in those aged <55 years.

Male vs female differences were greater when OA was defined by other than radiographic methods (i.e., clinical or self-report) for any, knee and hand OA (Table II). Only radiographic definition was used in studies of hip OA. In univariable meta-regression, there was an increase in RR males vs females of $+0.57$ for any OA ($P = 0.01$), $+1.03$ for knee OA ($P = 0.02$) and $+0.80$ (hand OA, $P < 0.0001$) when OA was defined using only radiographic methods compared to other methods, the effect of this being to decrease sex differences in prevalence when a purely radiographic definition was used.

Male vs female RRs were lower in predominantly Caucasian samples compared to non-Caucasian samples for any OA, hip OA and hand OA, but with very little difference for knee OA (Table II). For other quality measures, the effects of random vs non-random sample or adequate response rate ($\geq 50\%$) vs poor response rate ($<50\%$) were to cause an increase in the observed male vs female RRs for any OA and hip OA (in the former) and hip and hand OA (in the latter). The provision or non-provision of a reliability estimate for diagnosis did not change RR estimates. In univariable meta-regression, there were no significant associations observed between ethnicity, sample type, response rate, diagnostic reliability and lnRR. There was no significant effect of overall quality score on lnRR for any OA and other peripheral sites.

With multivariable meta-regression, the associations of explanatory variables with lnRR varied between OA categories (Table V). No explanatory variables were significantly associated with lnRR for prevalent hip OA (data not shown). For any OA, 70% of between-study heterogeneity (τ^2 reduction from 0.10 to 0.03) could be explained by the combination of method of OA definition, adequacy of response rate and ethnicity. These results for any OA remained unchanged after excluding a study[18] with an extremely large sample size ($n = 32{,}251$) from the analysis. This regression equation gives a predicted male vs female RR of 0.90 for any OA in an "ideal" study (radiographic definition, response rate $>50\%$) in a Caucasian population, very similar to the overall pooled estimate of 0.93. For knee OA, the combination of OA definition, ethnicity and provision of diagnostic reliability explained 55% of residual heterogeneity between studies (τ^2 reduction from 0.09 to 0.04). From this equation, the

Table V
Multivariable meta-regression of studies of prevalent OA

Variable	Any OA (9 studies*)			Knee OA (12 studies*)			Hand OA (13 studies*)		
	β	RR ratio†	P‡	β	RR ratio	P‡	β	RR ratio	P‡
OA definition									
X-ray only	0.56	1.75	0.001	0.92	2.51	0.001	1.25	3.49	<0.001
Other§		1.00			1.00			1.00	
Ethnicity									
Caucasian	−0.25	0.78	0.13	0.33	1.38	0.10	–	–	–
Other§		1.00			1.00		–	–	–
Sample									
Random	–	–	–	–	–	–	−0.91	0.41	0.002
Non-random§	–	–	–	–	–	–		1.00	
Response rate									
$\geq 50\%$	−0.42	0.65	0.01	–	–	–	0.78	2.18	0.012
$<50\%$/not stated§		1.00		–	–	–		1.00	
Reliability									
Provided	–	–	–	−0.26	0.77	0.09	–	–	–
Not provided§	–	–	–		1.00		–	–	–
Constant	0.01			−1.44			−1.26		

Results presented only for variables contained in the model of best-fit in each OA category, with cells for those not included in the model left blank. No significant associations were found for hip OA, therefore no data presented for this category. β-Regression coefficient.

*Number of studies providing subgroup data.

†Ratio of RR's for subgroups estimated as e^{β}.

‡P for significance for estimated change in RR for unit change in reference category.

§Reference category in each subgroup.

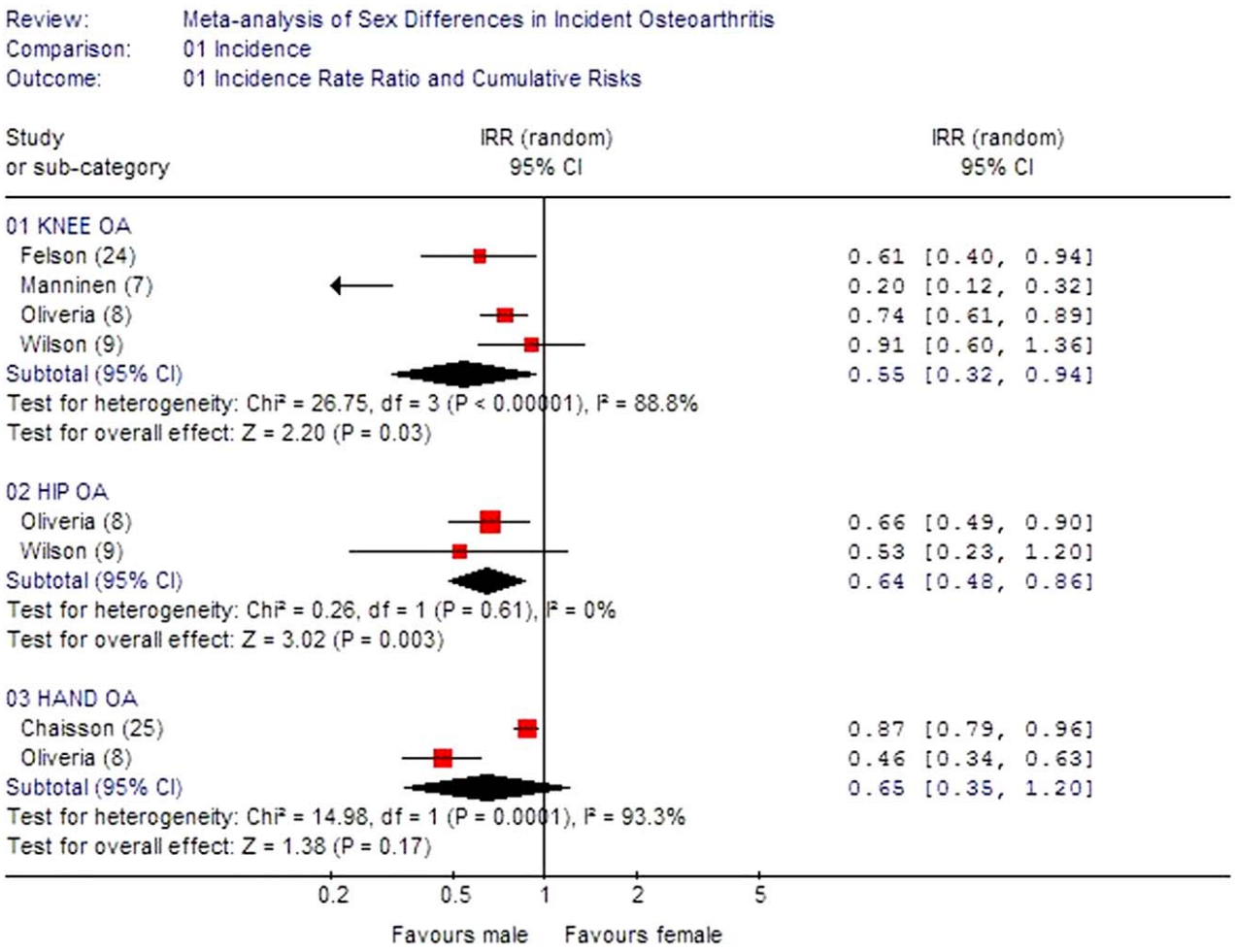

Fig. 3. Meta-analysis of sex differences in incident osteoarthritis. Studies identified by first author with reference citation number in parentheses.

predicted male vs female RR of 0.64 for an ideal study (radiographic definition, reliable measurement) in Caucasians is very similar to the pooled estimate of 0.63. In hand OA, 88% of residual between-study heterogeneity (τ^2 reduction from 0.08 to 0.01) was explained by the combination of OA definition, sample type and adequacy of response rate. Using this equation, the predicted male vs female RR for hand OA in an ideal study (radiographic definition, random sample, response rate $>50\%$) is 0.87, similar to the pooled estimate of 0.81.

SEX DIFFERENCE IN INCIDENCE OF OA

The meta-analysis for incident OA is presented in Fig. 3. In males, there was a statistically significant reduction in the incidence rate of knee OA (IRR 0.55, 95% CI 0.32–0.94, $P = 0.03$) and hip OA (IRR 0.64, 95% CI 0.48–0.86, $P = 0.003$), and a non-significant reduction in the incidence rate of hand OA (IRR 0.65, 95% CI 0.35–1.20, $P = 0.17$). There was significant between-study heterogeneity for knee and hand OA, but not for hip OA.

Examination of the funnel plots showed that there was non-symmetry for knee OA, hip OA and hand OA, but not for any OA (fig. 1). However, there were very few small studies in most categories. There was a relative paucity of studies with greater male vs female RRs in knee and hand OA, with the reverse seen in studies of hip OA.

SEX DIFFERENCES IN SEVERITY OF PREVALENT OA

These results are shown in Fig. 4. Prevalent knee OA was significantly more severe in females (female vs male pooled SMD 0.20, 95% CI 0.11–0.28, $P < 0.001$). These estimates did not change after excluding the single study without radiographic definition for OA (data not shown)[17]. There was no difference between males and females in the severity of prevalent hip OA (pooled SMD 0.02, 95% CI −0.07 to 0.10, $P = 0.65$) or prevalent hand OA (pooled SMD −0.03, 95% CI −0.11 to 0.05, $P = 0.43$). There was significant heterogeneity between studies in the pooled analyses for all three categories. In univariable meta-regression, age contributed significantly to the variability in SMDs between studies of knee OA ($\beta = 0.18$, $P < 0.001$) and hand OA ($\beta = 0.21$, $P < 0.001$) with a trend for hip OA ($\beta = -0.08$, $P = 0.08$). The effect of age in knee and hand OA was to increase the male vs female SMDs in people aged ≥ 55 years compared to those aged <55 years (Fig. 5). There were no significant effects of sample type,

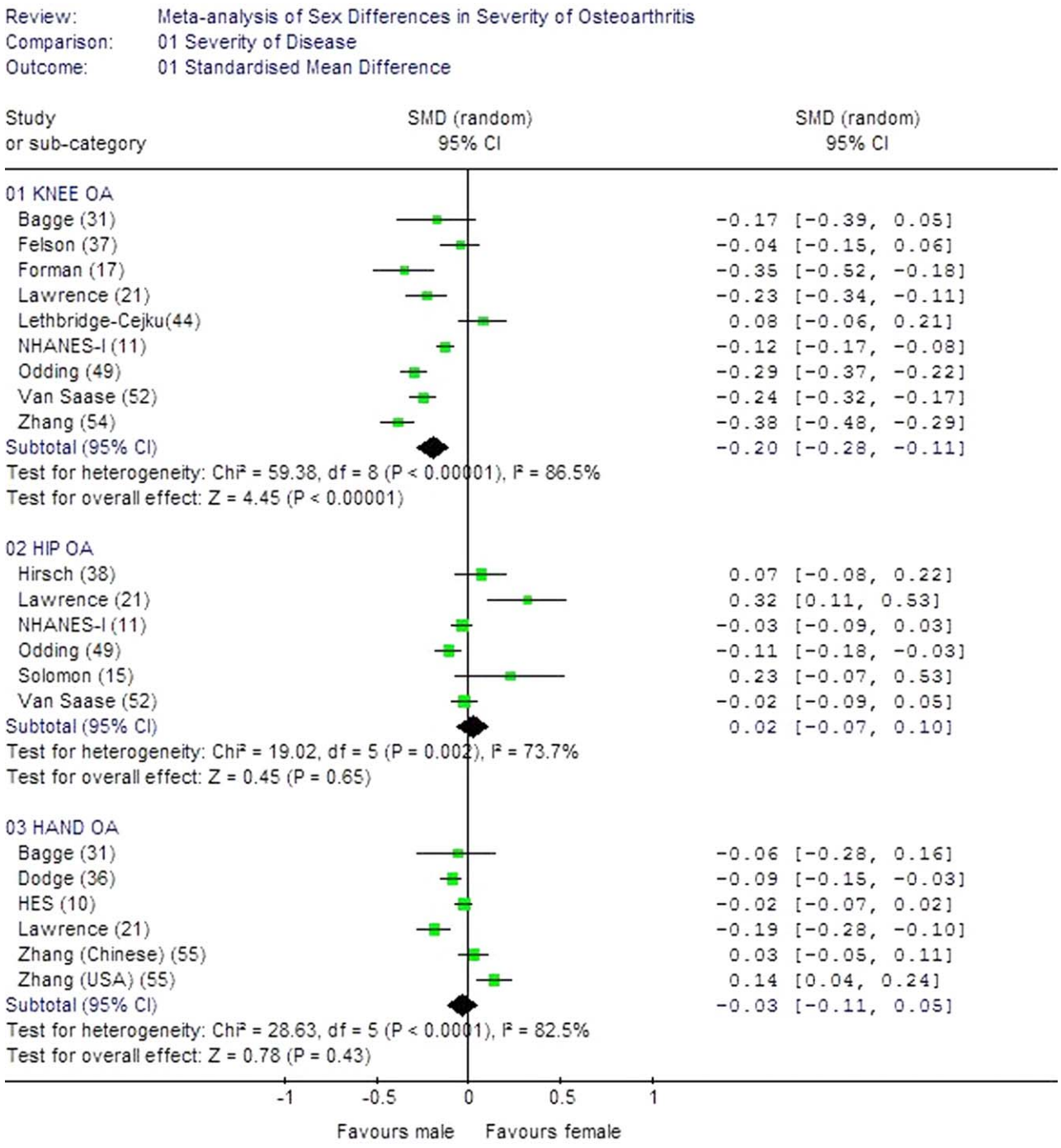

Fig. 4. Meta-analysis of severity and prevalent osteoarthritis. Studies identified by first author with reference citation number in parentheses.

response rates, diagnostic reliability and ethnicity on between-study variability.

Discussion

This meta-analysis provides evidence to support sex differences in prevalent and incident OA that are site-specific, with females generally at a higher risk. Heterogeneity in sex differences in prevalent OA was substantially explained by age, ethnicity, method of OA definition and sampling issues. We also found that females had more severe radiographic knee OA than males, although there were no significant sex differences in severity of hip and hand OA. Age was a significant contributor to the heterogeneity of effect of sex on severity in knee and hand OA, with larger sex differences in people aged $\geq$ 55 years.

There was significant risk reduction for knee and hand OA in males and this was consistent for both prevalence and incidence meta-analyses. However, the significant 36%

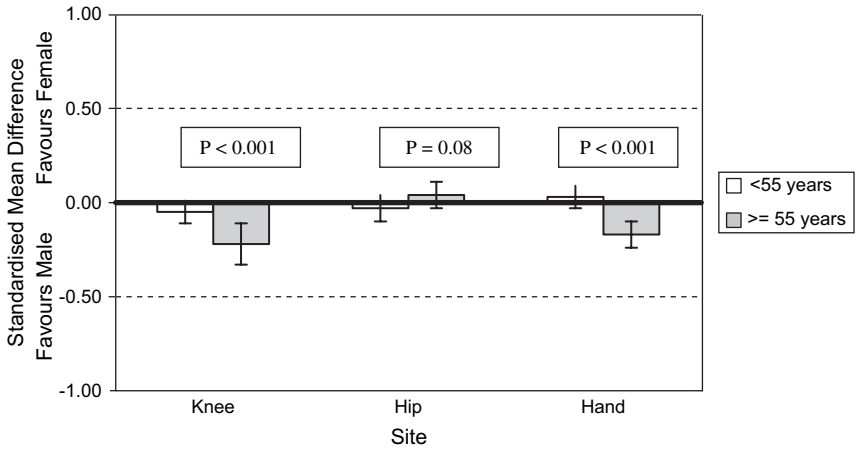

Fig. 5. The effect of age on sex differences in severity of osteoarthritis.

risk reduction for incident hip OA in males contrasts with the lack of a sex difference in prevalent hip OA. Sex differences in incidence studies are likely to be more reliable as they are free from the effect of differential survival between sexes that may be seen in prevalence studies. Although only two incidence studies of hip OA were available for pooling in the present analysis, the homogeneity of effect between these two large studies is also supportive of a true reduction in incident hip OA risk in males. Both studies were performed amongst Caucasian people with symptomatic OA, thus limiting conclusions to such populations. Moreover, such a sex difference in incident risk of hip OA is consistent with emerging data in the literature. In a large clinical sample of patients undergoing urography, females were found to have significantly greater decline in joint space width over a 4-year period[60]. In a randomly selected population-based older cohort, we have found that female sex was independently associated with lower hip cartilage volume in a cross-sectional analysis of a population-based sample of older people[61]. Longitudinal studies combining hip cartilage volume measures and standard radiographic measures may provide more definitive answers in this regard. Few data are available in the published literature to explain the sex differences observed in hand OA, with conflicting reports about associations of systemic factors such as hormonal status and obesity with hand OA in males and females[62,63]. Given that genetic factors play an important part in hand OA, it remains to be seen if the difference between sexes can be explained by interplay between genes and systemic/environmental factors. Findings for ''any OA'' were difficult to interpret because sex differences may have been masked by the variation in joint sites involved in different studies. In spine disease, the increased risk in younger males of cervical spine OA suggests the possibility of trauma as an explanation.

Heterogeneity between studies remained an important factor limiting the interpretation of our results for prevalent and incident OA. We were able to explore potential reasons for such heterogeneity for the former, but not the latter. We found that sex differences in knee and hand OA varied with age, such that prevalence was greater in females ≥ 55 years of age. The reasons for this site and age specificity are largely unknown but suggest an effect of the menopause[64], reflecting the effect of estrogen deficiency in earlier life. In a recent report, the sex difference in knee cartilage volume became greater after 50 years of age, suggesting a possible hormonal mediator of the sex difference and indicating the need for further research in this area[65]. Although estrogen may have a modulating effect on cartilage, the effects of sex hormones and growth factors in mediating such an age–sex interaction in OA risk are poorly understood[2,64]. We also speculate that the variation of such sex differences by age may also reflect the effect of trauma in earlier life in males although this remains to be explored further.

Apart from age, univariable meta-regression showed that method of OA definition also explained a substantial amount of the variation between studies of prevalent OA. The use of radiographic methods to define OA appeared to decrease the difference between sexes compared to self-report or clinical methods. Non-radiographic methods based on pain or other symptoms may result in over-diagnosis of OA. Female sex has been shown to be associated with hand pain after adjusting for age and radiographic scores for hand OA[66]. Women may be more likely to self-report OA. Greater pain levels in women may be mediated by specific forms of behaviour[67] that could lead to higher levels of self-report. Therefore, the use of non-radiographic methods may tend to exaggerate sex differences in prevalence due to reporting bias. Multivariable modeling showed that measures of study quality such as nature of sample, response rates and reliability, in variable combinations with definition and ethnicity, also explained some of the heterogeneity between studies of any, knee and hand OA. After accounting for such heterogeneity in the multivariable model, the predicted male vs female RRs for these categories were almost the same as the overall unadjusted pooled estimates. When combined with the small variation in risk ratios between the individual studies, this suggests that the observed degree of statistical heterogeneity between studies may to some extent be explained by the large samples in each category, and that the pooled estimates may be a reasonable reflection of the true sex differences.

Females had more severe radiographic knee OA than males, but no significant differences were found between sexes in the severity of hip and hand OA. These findings must be interpreted again in the light of heterogeneity between studies. We found that age may importantly contribute to heterogeneity in these analyses with sex differences being more pronounced in people aged ≥ 55

years, this effect being consistent for knee and hand OA. Other variables such as body mass index, physical activity, hormonal changes and bone factors may also explain this heterogeneity. In knee OA, heterogeneity cannot be explained by the method of OA diagnosis (self-report vs radiographic diagnosis) because the exclusion of the sole study without radiographic diagnosis did not change the results. Similarly, it is unlikely that the method of grading of severity is responsible for variability in effect between studies. Severity in almost all studies was graded using the standard Kellgren and Lawrence scale, which is weighted more towards the presence of osteophytes. It is possible, however, that different results may be obtained with a method of grading that is less dependent on the presence of osteophytes and more on the degree of joint space narrowing[68]. Heterogeneity may have also masked any sex differences in the severity of hip and hand OA, and thus we may be limited in our ability to draw firm conclusions in this regard.

The inclusion of only population-based studies, independent double data extraction and *a priori* specification of quality criteria are strengths of this meta-analysis. However, the possibility of publication bias is a potential limitation. Funnel plot asymmetry appeared to exist for the analyses of prevalent knee, hip and hand OA, indicating potential publication bias. It is difficult to conclude publication bias in the presence of heterogeneity of effect. However, if present, such bias may arise from the exclusion of smaller unpublished studies or non-English studies from the analysis. Such a bias may not be important in the case of hip OA, given that the overall pooled result is towards the null. In the case of knee and hand OA, the effect of publication bias is that male vs female differences found in our analysis may be slight overestimates, and the effect of inclusion of any unpublished small studies may be to slightly attenuate but is unlikely to abolish the sex differences due to the large samples included.

In conclusion, we provide meta-analytic evidence for a greater risk in females for prevalent and incident knee and hand OA and incident hip OA. No significant sex differences were observed for prevalent hip OA. We also found a higher risk for prevalent cervical spine degeneration in males aged <55 years. Females also tended to have more severe knee OA than males. Sex differences in severity were stronger among people aged ≥ 55 years. Thus, there is some basis for further exploration of factors responsible for sex differences in peripheral joint sites and possibly in the cervical spine. Further studies into these sex differences have the potential to increase understanding mechanisms underlying this common disease.

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Abbreviations

HES: Health Examination Survey.
lnRR: Natural Logarithm of Risk Ratio.
IRR: Incidence Rate Ratio.
NHANES: National Health and Examination Survey.
OA: Osteoarthritis.
ROA: Radiographic Osteoarthritis.
RR: Risk Ratio.
SE: Standard Error.
SMD: Standardized Mean Difference.